

Ischemia Detection using Perfusion MRI
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1. Perfusion imaging to detect myocardial ischemia

Myocardial ischemia occurs when insufficient blood flow, or perfusion, to the myocardium results in inadequate delivery of oxygen as well as inadequate removal of metabolites. These conditions may occur at rest due to insufficient oxygen supply (supply ischemia) or at stress due to a failure to sufficiently accommodate increased oxygen demand (demand ischemia). Coronary artery stenosis is a common cause of insufficient myocardial perfusion reserve and demand ischemia, with clinical symptoms typically appearing as angina and ST segment deviation on ECG predominantly at stress. Noninvasive imaging of perfusion defects at stress is widely used for the detection of significant coronary stenoses.

Numerous imaging modalities can be used to detect myocardial ischemia by perfusion assessment. The most widely used myocardial perfusion modality is SPECT imaging with ^{201}Tl or $^{99\text{m}}\text{Tc}$ -labeled agents, which are radiotracers that are rapidly taken up by and slowly cleared from the myocardium after intravenous administration. While SPECT is the standard clinical test for myocardial perfusion imaging (1), limitations of this technique include attenuation artifacts from soft tissue and relatively low spatial resolution. PET imaging with ^{13}N -labeled ammonia or ^{15}O -labeled water are more accurate (2;3), however these methods are also more expensive and are not widely available. Myocardial contrast echocardiography (MCE) can also be used for myocardial perfusion imaging (4), but this technique is not yet widely established and can be limited by poor acoustic windows. MRI offers several different methods for imaging myocardial perfusion, including first-pass contrast-enhanced imaging, blood oxygen level dependent (BOLD) imaging, and, in small animal models, arterial spin labeling (ASL). BOLD and ASL have the advantages that they do not require the use of exogenous contrast media, however they are still in the early stages of development and evaluation.

2. First-pass MRI

First-pass contrast-enhanced imaging is the most popular of the MRI methods for myocardial perfusion assessment. First-pass imaging was initially developed in the late 1980's, and is a tracer kinetic method based on using rapid T1-weighted imaging to detect the first passage of a T1-shortening contrast agent (Gd-DTPA) bolus as it flows through the left ventricular cavity and myocardial microcirculation (5). Example images demonstrating first-pass MRI in a normal subject are shown in Figure 1, where the arrival of contrast media in the right ventricle, lungs, left ventricular cavity, and left ventricular myocardium can be seen as a function of time. The spatial resolution of first-pass MRI is seen to be relatively high, and can distinguish transmural differences in perfusion. Time-intensity curves for the left ventricle (LV) cavity, normal myocardium, and ischemic myocardium from a patient with coronary artery disease are shown in Figure 2.

For the clinical application of ischemia detection in patients with suspected coronary artery stenoses, first-pass MRI is typically applied both during pharmacological vasodilation (stress) and at rest. The detection of stress-induced demand ischemia

appears as a lack of contrast enhancement in the territory supplied by a stenosed artery in first-pass images acquired during adenosine or dipyridamole infusion (Figure 2, arrow). It is important to realize, however, that stress-induced demand ischemia is not the only potential cause of a lack of contrast enhancement. This finding could also appear due to myocardial infarction or artifact, and the differential is usually clarified by the acquisition of additional non-stress (rest) first-pass images and by also acquiring inversion-recovery images to detect delayed hyperenhancement. With myocardial infarction, lack of contrast enhancement is seen at rest on first-pass images and delayed hyperenhancement is seen on inversion recovery images. With artifact, lack of contrast enhancement is seen at rest on first-pass images however delayed hyperenhancement is not seen on inversion recovery images. For true demand ischemia, lack of contrast enhancement is seen at stress on first-pass images but not at rest, and delayed hyperenhancement is not seen on inversion recovery images.

3. Pulse sequences for first-pass MRI

While first-pass MRI has been under development and optimization for more than 15 years, some technical issues such as optimal pulse sequence and how and whether to quantitatively analyze the images are still the subject of active investigation. Regarding the optimal pulse sequence, saturation-recovery fast gradient echo (also referred to as TurboFLASH) is the most widely used technique (6). However, hybrid fast gradient echo – echo planar imaging (GRE-EPI) sequences (7;8) acquire data more rapidly and steady state free precession (SSFP) sequences (9) generate greater contrast. The importance of rapid data acquisition is that greater slice coverage is enabled and less cardiac motion occurs during the data acquisition period. Also, fat suppression is more effective for shorter data acquisition periods. The importance of greater image contrast could be higher sensitivity for detecting perfusion defects, although this is yet to be shown clinically. Interestingly, recent studies attempting to clarify the pulse sequence question have reported conflicting results, with one study in patients with coronary artery disease favoring GRE-EPI (10) and another study in volunteers favoring SSFP (11). Furthermore, all of the sequences continue to evolve particularly with the advent of parallel imaging.

4. Quantitative analysis of first-pass MRI

The importance and practicality of quantitatively analyzing first-pass images is also the subject of debate, although recent studies support the benefit of quantitative analysis versus visual interpretation (12;13). To perform a quantitative analysis, time-intensity curves such as those shown in Figure 2 must be derived from the images. However, if breathholding is not successful during image acquisition, then respiratory motion leads to spatial misregistration of the time series of images and time consuming image registration requiring some degree of manual supervision is needed to generate time-intensity curves. If time-intensity curves are generated, quantitative model-based deconvolution methods can be used to estimate perfusion in units of ml/g/min (14) or, by solving the modified Kety equations, the flow – extraction fraction product can be estimated (15). For both of these methods, estimates of the input function as well as the tissue function are required, where the tissue function corresponds to the signal intensity in the myocardium and the input function typically corresponds to the signal intensity in

the LV cavity blood pool. Semi-quantitative methods use simpler metrics derived from the time-intensity curves such as the ratio of the tissue function upslope to the input function upslope. Methods that utilize the input function for image analysis generally require the use of a relatively low contrast agent concentration, such as 0.025 mmol/kg, since the signal from the LV cavity is not linear with contrast agent concentration for significantly higher concentrations. This constraint limits the signal-to-noise ratio of the myocardium during the first pass of the contrast agent.

5. Clinical studies evaluating first-pass MRI for ischemia detection

Clinical studies using first-pass MRI for ischemia detection have demonstrated promising results. Using older hardware and pulse sequences, sensitivities and specificities were variable, with sensitivities ranging from 65 – 92% and specificities ranging from 75 – 100% (16). Using newer methods, more consistent data demonstrate that both sensitivity and specificity are typically around 85 – 90%. For example, Schwitter et al studied 48 patients and 18 volunteers using GRE-EPI first-pass MRI, PET, and x-ray coronary angiography. Using the ratio of the tissue function and input function upslopes as an index of perfusion, the sensitivity and specificity of MRI were 91% and 94%, respectively, compared to PET, and 87% and 85%, respectively, compared to coronary angiography (17). Similarly, Nagel et al studied 84 patients referred for coronary angiography at rest and during vasodilation. Using the same perfusion index (ratio of upslopes), the sensitivity and specificity vs. coronary angiography were 88% and 90%, respectively (12). Finally, a recent study by Ishida et al achieved a sensitivity of 90% and specificity of 85% compared to coronary angiography in 104 patients (18). This study also showed a significantly higher area under the receiver operator characteristic curve for first-pass MRI compared to SPECT for 69 patients who additionally underwent SPECT.

6. Current and future directions

Interesting new directions include the development of dual-contrast first-pass sequences and first-pass MRI at a magnetic field strength of 3T. In dual-contrast sequences (19), a relatively high contrast agent concentration is used and multislice imaging is performed. In addition to sampling multiple slices with a typical sequence, an additional slice for the input function is acquired which has altered image contrast and lower spatial resolution. Specifically, the input function slice is acquired using parameters where signal intensity is linear with contrast agent concentration for the high concentrations found in the blood pool, whereas the remaining slices use parameters where signal intensity is linear for the lower concentrations found in the myocardium. Lower spatial resolution can be used for the input function slice in order to reduce the time spent for input function sampling. Using this approach, a quantitative analysis can be performed using images acquired with high contrast agent concentrations and, subsequently, higher myocardial signal-to-noise ratio.

The possibility of acquiring first-pass MR images of the human heart at 3T has also recently been explored (20). The advantage of cardiac MR at 3T is that, in general, 3T provides higher signal-to-noise ratio than 1.5T. However, cardiac MRI at 3T may also generate more artifacts than 1.5T. Initial findings in normal subjects suggest that contrast enhancement may increase by around 70% at 3T compared to 1.5T without a

significant increase in artifact. Additional studies are warranted in first-pass MR at 3T and in general cardiac MR at 3T.

7. Summary

First-pass MRI is a tracer kinetic method for perfusion assessment where rapid T1-weighted imaging is used to detect the T1-shortening affect of a contrast agent after IV bolus injection. Detection of demand ischemia and corresponding coronary artery stenosis can be accomplished in patients by first-pass MRI during pharmacological vasodilation. Recent clinical studies using these techniques report sensitivities and specificities of around 85 – 90%, using x-ray coronary angiography or PET as a standard. Areas of continued investigation in first-pass MRI include pulse sequence optimization, image analysis techniques, dual-contrast sequences, and imaging at 3T.

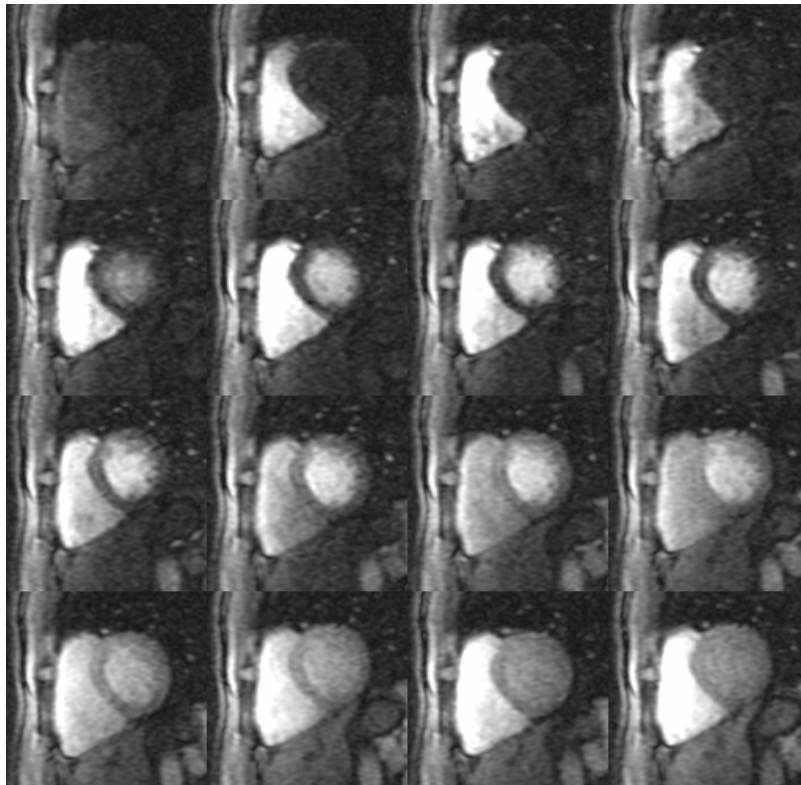


Figure 1. Example first-pass MR images of one short-axis slice of a normal subject, with time proceeding from upper left to lower right. The time between each image is one heartbeat. Before the arrival of the contrast agent bolus (upper left), the entire heart appears dark. Over time after an intravenous bolus injection, the contrast agent appears first in the right ventricle, then the arteries of the lung, then the left ventricular cavity, and finally in the left ventricular myocardium. Normal myocardium enhances uniformly.

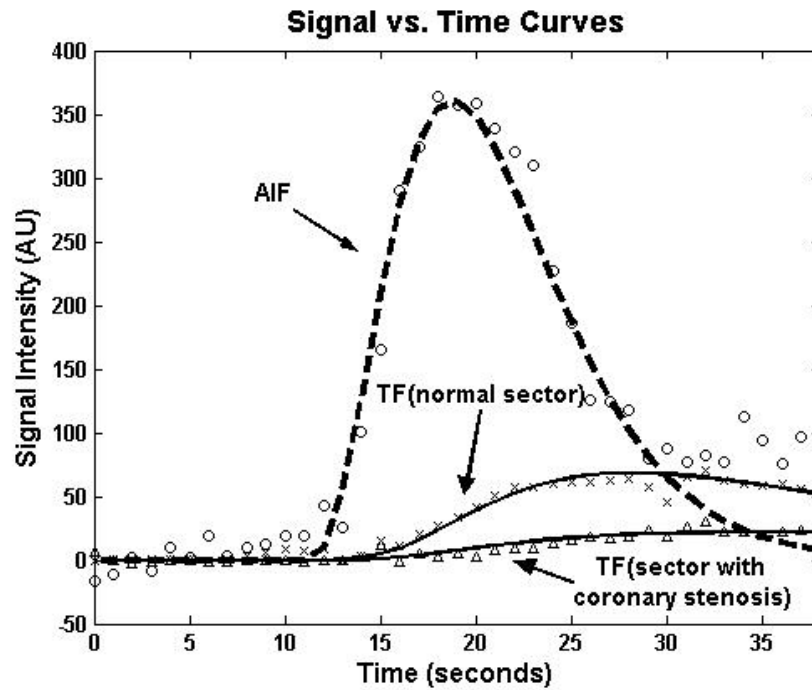


Figure 2. Example time-intensity curves (TICs) from a patient with a significant coronary artery stenosis. The TIC from the LV cavity represents the arterial input function (AIF), which is used for quantitative or semiquantitative analysis. Also shown are TICs from normal and ischemic regions. The ischemic region displays reduced contrast enhancement.

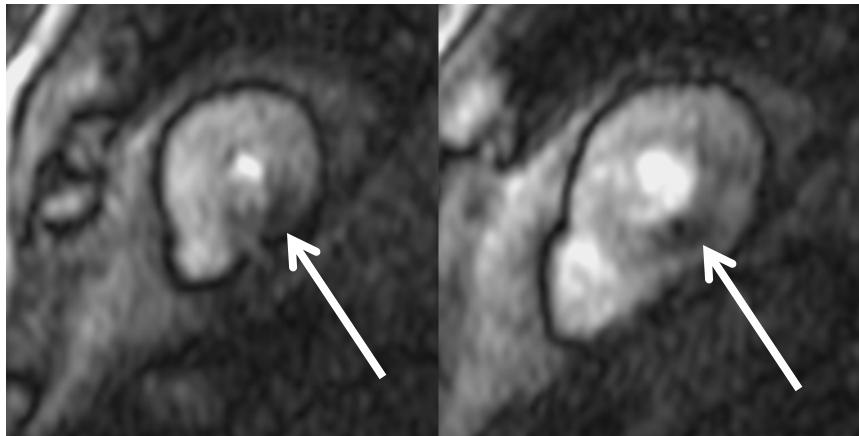


Figure 3. Example first pass images at peak contrast enhancement demonstrating a lack of contrast enhancement in an ischemic region (arrow) induced during pharmacological vasodilation.

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